REMARKS

Status of Claims and Amendment

Claims 1-3, 5-8, 10, and 12 have been amended. Claims 4 and 9 have been canceled. Claims 1-3, 5-8, 10, and 11 are all the pending claims being examined in the application. Claims 12-16 are withdrawn as being directed to a non-elected invention. Claims 1-11 are rejected.

Claim 1 has been amended to even more clearly recite that the expression vector comprises a "polynucleotide encoding for a polypeptide of SEQ ID NO:9" which "hydroxylates" the 24-position of an oleanane type triterpene. Support for the amendments to claim 1 may be found at least at page 4, paragraph [0007] of the specification.

Claims 2 and 7 has been amended to replace "represented by" with "of" as suggested by the Office Action.

Claims 3 and 8 has been amended to incorporate the limitations of claims 4 and 9, i.e., to recite "wherein the host is a microorganism."

Claim 5 has been amended to change the claim dependency from claim 4 to claim 3.

Claim 6 has been amended to delete reference to the hybridization condition, and to recite a "co-expression vector" comprising a "polynucleotide encoding for the polypeptide of SEQ ID NO:9." Support for the amendments to claim 6 may be found at least at page 4, paragraph [0007] and page 13-14, paragraph [0014] of the specification.

Claim 12 has been amended to recite "a polypeptide of SEQ ID NO:9" to be consistent with claim 1. Support for the amendments to claim 12 may be found at least at page 4, paragraph [0007] of the specification.

In addition, the title has been amended to recite "Expression Vector Encoding a Triterpene Hydroxylase Polypeptide", as suggested by the Office Action in response to an objection to the specification.

No new matter is added.

Claim to Priority

Applicants thank the Examiner for acknowledging Applicants' claim to priority of Japanese Application No. 2004-049123 filed February 25, 2004, as well as receipt of a certified copy of the priority document.

Information Disclosure Statements

Applicants thank the Examiner for acknowledging the Information Disclosure Statements filed August 25, 2006 and December 15, 2006, by returning signed copies of the PTO/SB/08 forms submitted therewith indicating that all references have been considered.

Election/Restriction

The Examiner has acknowledged Applicants' election with traverse of Group I (claims 1-11) in the Response filed February 25, 2008. The Examiner asserts that because none of the elected claims is in condition for allowance, consideration of claims 12-16 for rejoinder with the elected claims of Group I is not yet required.

Response To Objection To The Specification

The Examiner appears to object to the title of the invention as not being sufficiently descriptive of the claimed invention. The Examiner suggests amending the title to "Expression Vector Encoding a Triterpene Hydroxylase Polypeptide."

In response, Applicants have amended the title as suggested by the Examiner.

Withdrawal of the grounds of objection is respectfully requested.

Response To Claim Objections

Claim 1 is objected to as generally being unclear. The Examiner suggests amending claim 1 in the following manner to more clearly identify each part of the claimed expression vector.

"An expression vector having:

1) a polynucleotide: i) which hybridizes with a complementary chain of the polynucleotide represented by SEQ ID NO:8 under a stringent condition and ii) encodes a polypeptide that has the activity of hydroxylating the 24-position of an oleanane type triterpene.

Claim 6 is objected to for similar reasons, and the Examiner suggests amending claim 6 in the following manner to more clearly identify each part of the claimed expression vector.

"An expression vector having:

1) a polynucleotide: i) which hybridizes with a complementary chain of the polynucleotide represented by SEQ ID NO:8 under a stringent condition and ii) encodes a polypeptide that has the activity of hydroxylating the 24-position of an oleanane type triterpene; and

2) a β-amyrin synthase gene."

In response, Applicants have amended claims 1 and 6 in a manner similar to the Office Action's suggestions.

Withdrawal of the grounds of objection is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-10 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

a) The Office Action asserts that claims 1 and 6 are indefinite because the recitation "a stringent condition" is not clearly defined in the specification, i.e., the specification does not define what conditions constitute "stringent". The Office Action acknowledges that the specification at the paragraph bridging pages 9-10 discloses an "illustrative" example of a "stringent condition", but that the disclosure is only an example of a "stringent" condition. The Office Action requests that Applicants clarify the meaning of "a stringent condition."

b) In addition, the Office Action asserts that the recitation "polynucleotide represented by SEQ ID N0:8" in claims 1 and 6 is unclear because of the term "represented" with respect to SEQ ID N0:8. The Office Action asserts that Webster's online dictionary defines "represent" as an example so that the Office Action is unclear whether the polynucleotide is limited to the sequence of SEQ ID NO:8 or SEQ ID NO:8 is merely an example.

In response, Applicants note that the pending claims prior to the present amendment clearly define what Applicants consider to be the claimed invention. However, solely to advance prosecution of the present application, the claims have been amended in the following manner.

Claims 1 and 6 have been amended to delete reference to the hybridization conditions, and to recite an expression vector or co-expression vector comprising "a polynucleotide encoding for a polypeptide of SEQ ID NO:9."

In addition, claims 2 and 7 have been amended to replace "represented by" with "of."

Claims 4 and 9 have been canceled. Accordingly, the rejection with regard to claims 4 and 9 is rendered moot.

Withdrawal of the rejection under § 112, second paragraph, is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 101 35 U.S.C. § 101

Claims 3 and 8 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The Office Action asserts that the claims encompass a human being because a "transformant" is prepared by transforming a host, and the specification at page 13, paragraph [001] states "[a]s examples of the host, a microorganism, a plant, an animal and the like can be cited, though not particularly limited." Human beings are not patentable subject matter under U.S. law.

In response, and solely to advance prosecution of the present application, claims 3 and 8 have been amended to recite that the host is a microorganism.

Reconsideration and withdrawal of the rejection under § 101 is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 112, First Paragraph

1. Rejection of Claims 1-10 for Lack of Written Description

Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

A. The Office Action states that the phrase "a polynucleotide which hybridizes with a complementary chain of the polynucleotide represented by SEQ ID NO:8" is interpreted to encompass fragments of the polynucleotide represented by SEQ ID NO:8 that may be as few as two contiguous nucleotides. However, according to the Office Action, the specification discloses only one polypeptide that is encoded by a polynucleotide of SEQ ID NO:8.

B. The Office Action also states that the phrase "the activity of hydroxylating the 24-position of an oleanane-type triterpene" is interpreted to encompass hydroxylating position 24 of any triterpene considered to be an "oleanane-type" triterpene. However, according to the Office

Action, the polypeptide encoded by the polynucleotide of SEQ ID NO:8 only hydroxylates position 24 of β-amyrin and sophoradiol.

C. In addition, the Office Action states that the phrase "β-amyrin synthase gene" is interpreted to mean any nucleic acid that encodes a polypeptide having β-amyrin synthase activity. However, the Office Action asserts that the specification only discloses a pea-derived β-amyrin synthase gene PSY as "a single representative species of the recited β-amyrin synthase gene."

The Office Action appears to assert that because the art is unpredictable, written description of a claimed genus cannot be achieved by disclosing only one, or two species within the genus.

With regard to item A, Applicants note that the revised PTO Guidelines (published March 25, 2008) indicate that for products claimed by their function, it is required that all applications provide an identification of the common characteristics of the claimed molecule, e.g., structure, physical and/or chemical properties, characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicants were in possession of the claimed genus (see Example 10 of revised PTO Guidelines). Alternatively, when an art-recognized structure-function correlation is not present, the written description requirements under 112, first paragraph are satisfied for a nucleotide that encodes a polypeptide with at least 85% amino acid sequence identity to a particular sequence even when only that particular sequence (a single species) is disclosed (see Example 11 of revised PTO Guidelines).

In this case, Applicants note that a polynucleotide that encodes for a polypeptide of SEQ ID NO:9, i.e., SEQ ID NO:8, is disclosed in the specification (see paragraph [0007] of the

specification), and that the polynucleotide may show a homology of at least 90% to SEQ ID NO:8 (see paragraphs [0011] and [0007] of the specification). Also, as acknowledged by the Office Action at page 8, 2nd full paragraph, SEQ ID NO:8 is the "only…single representative species of the recited polynucleotides encoding a polypeptide that [has] the activity of hydroxylating the 24-position of an oleanane type triterpene" disclosed in the specification.

Accordingly, and solely to advance prosecution of the present application, Applicants have amended claim 1 to recite an expression vector "comprising a polynucleotide encoding for a polypeptide of SEQ ID NO:9."

In addition, with regard to claim 6, Applicants note that the polynucleotides that may hybridize with a complementary chain of the polynucleotide of cytochrome P-450 gene CYP93E1 (SEQ ID NO:8), includes polynucleotides with one or more nucleotides that are deleted, substituted, inserted, or added in the polynucleotide sequence of SEQ ID NO:8. (See paragraph bridging pages 10-11 of the specification). Nevertheless, solely to advance prosecution of the present application, claim 6 has been amended to recite an "co-expression vector comprising a polynucleotide encoding for a polypeptide of SEQ ID NO:9", and delete recitation to the hybridization condition and the activity of hydroxylating the 24-position of an oleanane type triterpene.

With regard to item B and the Office Action's assertions concerning the hydroxylating activity of the polypeptide encoded by the polynucleotide of SEQ ID NO:8, Applicants note that one of ordinary skill in the art would understand from reading the disclosure in specification that the polypeptide encoded by the polynucleotide of SEQ ID NO:8 has the activity of hydroxylating the 24-position of an oleanane type triterpene.

With regard to item C and the Office Action's assertions concerning β-amyrin synthase gene, Applicants note that pursuant to M.P.E.P. § 2163, "there is an inverse correlation between the level of skill and knowledge in the art and the specificity of the disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification." In this regard, Applicants note that the structure and function of the β-amyrin synthase gene is commonly known in the art to be involved in the biosynthesis of β-amyrin, one of the most commonly occurring triterpenes in nature. (See Kushiro et al., Eur. J. Biochem. 256: 238-244 (1998))[1].

Reconsideration and withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

Rejection of Claims 1-10 for Lack of Enablement

Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an expression vector comprising a polynucleotide encoding the polypeptide of SEQ ID NO:9 and optionally further comprising the pea-derived β-amyrin synthase gene PSY (Morita et al., *Eur. J. Biochem.*, 267, 3543-3460, 2000) and an isolated host cell transformed with the expression vector, allegedly does not reasonably provide enablement for all expression vectors as broadly encompassed by the claims.

The Office Action appears to assert the same reasons as discussed above under the written description rejection. In other words, the Office Action asserts that the broad scope of claimed expression vectors is not enabled by the disclosure, particularly with regard to the scope

[1] In accordance with M.P.E.P. § 609.05(c), the document cited herein in support of Applicants' remarks is being submitted as evidence directed to an issue raised in the Official Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08A & B is believed to be necessary.

of polynucleotides that encode a polypeptide that "has the activity of hydroxylating the 24-position of an oleanane type triterpene" and β-amyrin synthase genes. Specifically, the Office Action asserts that the specification fails to provide specific guidance regarding those nucleotides of SEQ ID NO:8 that may be altered by substitution, addition, insertion, and/or deleted with to encode a polypeptide that maintains the desired activity of "hydroxylating the 24-position of an oleanane type triterpene" or those nucleotides of the pea-derived β-amyrin synthase gene PSY that may be altered by substitution, addition, insertion, and/or deletion to encode a polypeptide that maintains the desired activity of β-amyrin synthase.

With regard to claims 3 and 8, the Office Action asserts that the specification fails to provide guidance, such as a working example, for generating transgenic animals transformed with the claimed expression vector. The Office Action asserts that while there is no requirement that the specification disclose a working example, the state of the art represented by the references cited in the Office Action (see pages 14-15 of the Office Action), indicates that gene transfer was an unpredictable and underdeveloped art at the time of the invention.

Accordingly, the Office Action concludes that in view of the *Wands* factors, one of ordinary skill in the art would require undue experimentation to make and/or use the entire claimed genus of the invention.

In response, Applicants note that "[d]etailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the claimed invention." M.P.E.P. §2164. Also, "[a] patent need not teach, and preferably omits, what is well known in the art." M.P.E.P. §2164.01. "The fact experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." Id. "As long as the specification discloses at least

one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." M.P.E.P. §2164.01(b). Further, "[t]he scope of enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required." M.P.E.P. §2164.03.

Applicants note that the specification provides ample disclosure to enable one of ordinary skill in the art to make and use the claimed invention. For instance, page 11-13, discloses that the claimed polynucleotide may be obtained by commonly known hybridization methods or a PCR method using a part or entire portion of the nucleotide sequence as a probe. In addition, the paragraph bridging pages 12-13 discloses that the claimed polynucleotide may be also obtained by commonly known chemical synthesis based on the nucleotide sequence, as referenced by the method disclosed in *Gene*, 60(1): 115-127 (1987). Page 15 to the top of page 18 discloses how to transfer a recombinant vector comprising the claimed polynucleotide into host cells, and how to select for a transformant made from such methods. Induction of such a transformant is discussed at page 17, paragraphs [0020]-[0021], and production of a 24-position hydroxylated compound from culturing such a transformant is discussed at page 18, paragraph [0022] to page 19, paragraph [0025] of the specification. Detection of the enzyme hydroxylating activity at the 24-position is disclosed at pages 24-28 of the specification. Production of the claimed expression vectors and detection of 24-position hydroxylated compounds is further discussed at page 20, paragraph [0026] to page 22, paragraph [0033], and exemplified in Example 1. In addition, as discussed above, the structure and function of the β-amyrin synthase gene is commonly known in the art. (See Kushiro et al., Eur. J. Biochem. 256: 238-244 (1998)).

Nevertheless, solely to advance prosecution of the present application, the claims have been amended in the following manner.

Claims 1 and 6 have been amended to delete reference to the hybridization conditions, and to recite an expression vector or co-expression vector comprising "a polynucleotide encoding for a polypeptide of SEQ ID NO:9."

Applicants note that the Board of Patent Appeals and Interferences (BPAI) has recognized that mere routine experimentation is required to enable the full scope of an Applicants' claims reciting nucleic acids encoding proteins at least 80% identical to the disclosed amino acid sequence claimed. Thus, the BPAI has found claims having scope broader than the exact amino acid or nucleotide sequence disclosed should not be rejected under the enablement requirement of 35 U.S.C. § 112, first paragraph.

In addition, claims 3 and 8 have been amended to incorporate the limitations of claims 4 and 9, i.e., to recite "wherein the host is a microorganism."

Claims 4 and 9 have been canceled. Accordingly, the rejection with regard to claims 4 and 9 is rendered moot.

Reconsideration and withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

Response To Rejection of Claim 11 for Lack of Enablement

Claim 11 is rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

The Office Action states that the claimed invention is drawn to a novel yeast strain. The Office Action asserts that since the strain is essential to the claimed invention, it must be obtained by a repeatable method set forth in the specification or otherwise be readily available to

the public. In this regard, the Office Action asserts that a repeatable method for obtaining the mutant yeast strain is not fully disclosed, and it is unclear whether the strain is readily available to the public. However, the Office Action asserts that the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the strain.

The Office Action notes that Applicants appear to have deposited the organism but there is no indication in the specification as to public availability. The Office Action states that:

(1) If a biological deposit was made under the terms of the Budapest Treaty, Applicants may address this rejection by providing an affidavit or declaration or a statement by Applicants' attorney, that the deposit was made under the terms of the Budapest Treaty and that the strain will be irrevocably and without restriction released to the public upon issuance of a patent.

(2) If a biological deposit was made but not under the terms of the Budapest Treaty, the Office Action states that Applicants must provide assurance or compliance by an affidavit or declaration, or a statement by Applicants' attorney of record assuring that: (a) during the pendency of this application , access to the invention will be afforded to the Commissioner upon request; (b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent; (c) the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and (d) the deposit will be replaced if it should ever become inviable.

In response, Applicants note that a biological deposit was made for the transformed yeast as disclosed at page 21, paragraph [0029] of the specification. In addition, Applicants submit herewith the attached certificate of the Deposit under the terms of the Budapest Treaty and a Statement of Availability to show that the enablement requirement is met.

Reconsideration and withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 102(b)

Claim(s) 1-3 are rejected under 35 U.S.C. § 102(b) as being anticipated by Steele et al. (Arch. Biochem. Biophys. 367:146-150, 1999; "Steele") as evidenced by Shibuya et al. (FEBS J. 273:948-959, 2006; "Shibuya").

The Office Action asserts that Steele teaches an insect cell comprising a baculovirus expression vector with a nucleic acid comprising a CYP93EI gene that is 99.7% identical and 99.8% similar to SEQ ID NO:8 of the claimed invention. Shibuya is asserted by the Office Action for showing that the polypeptide encoded by the CYP93E1 gene of Steele encodes a polypeptide that hydroxylates position 24 of β-amyrin.

In response, Applicants note that Steele does not explicitly or inherently disclose the presently claimed expression vector comprising a polynucleotide encoding for a polypeptide of SEQ ID NO:9.

Reconsideration and withdrawal of the rejection under § 102(b) is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 103

Claims 4-5 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Steele in view of La Rosa et al. (US Patent Application Publication 2004/0031072 Al; "La Rosa") and Schopfer et al. (*FEBS Lett.* 432:182-186, 1998; "Schopfer").

The Office Action asserts that Steele does not teach a microorganism or a yeast as an expression host. However, the Office Action asserts that La Rosa suggests recombinant expression in *E. coli* of a polynucleotide, SEQ ID NO:100510, that is 99.7% identical and 99.8% similar to claimed SEQ ID NO:8.

Schopfer is asserted by the Office Action for teaching recombinant expression of a soybean cytochrome P450-dependent enzyme in a yeast host cell optimized for expression of cytochrome P450 enzymes.

Thus, the Office Action concludes that it would have been obvious to one of ordinary skill in the art to combine the teachings of Steele, La Rosa, and Schopfer to transform an E. coil or yeast host cell with an appropriate expression vector comprising the polynucleotide of Steele.

The Office Action asserts that one of ordinary skill in the art would have been motivated to make such a combination because of the express teachings of La Rosa or because the yeast of Schopfer is optimized for cytochrome P450 recombinant protein expression, and have a reasonable expectation of success to transform an E. coil or yeast host cell with an appropriate expression vector.

Initially, Applicants note that in order to establish a *prima facie* case of obviousness, "the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. § 2143. Also, pursuant to M.P.E.P. § 2141.02, "the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole." This means that "[i]n determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." Id.

In response, Applicants note that neither Steele, La Rosa, nor Schopfer teaches or suggests the presently claimed transformant because none of the cited documents teaches or suggests a polynucleotide encoding for a polypeptide of SEQ ID NO:9, i.e., SEQ ID NO:8.

Also, as acknowledged by the Office Action, Steele does not teach a microorganism or a yeast as an expression host (see page 19, paragraph [15] of Office Action).

Reconsideration and withdrawal of the rejection under § 103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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